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Drugs for preventing postoperative nausea and vomiting in adults after general anaesthesia: a network meta-analysis (Protocol)

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TABLE OF CONTENTS

Drugs for preventing postoperative nausea and vomiting in adults after general anaesthesia: a network meta-analysis

Stephanie Weibel[1], Yvonne Jelting[1], Nathan Leon Pace[2], Gerta Rücker[3], Diana Raj[4], Maximilian S Schaefer[5], Insa Backhaus[6], Peter Kienbaum[5], Leopold HJ Eberhart[7], Peter Kranke[1]

[1]Department of Anaesthesia and Critical Care, University of Würzburg, Würzburg, Germany. [2]Department of Anesthesiology, University of Utah, Salt Lake City, UT, USA. [3]Institute for Medical Biometry and Statistics, Faculty of Medicine and Medical Center - University of Freiburg, Freiburg, Germany. [4]Department of Anaesthesia, Intensive Care Medicine and Pain Medicine, Queen Elizabeth University Hospital, Glasgow, UK. [5]Department of Anaesthesiology, University Hospital Düsseldorf, Düsseldorf, Germany. [6]Department of Public Health and Infectious Diseases, Sapienza University of Rome, Rome, Italy. [7]Department of Anaesthesiology & Intensive Care Medicine, Philipps-University Marburg, Marburg, Germany

Contact address: Peter Kranke, Department of Anaesthesia and Critical Care, University of Würzburg, Oberduerrbacher Str. 6, Würzburg, Germany. kranke_p@ukw.de.

A B S T R A C T

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

1. To compare the efficacy and safety of different prophylactic pharmacological interventions (antiemetic drugs) either against no treatment, placebo or against each other (as mono- or combination prophylaxis) for the prevention of postoperative nausea and vomiting in adults undergoing any type of surgery under general anaesthesia.

2. To explore the best dose or dose range of the antiemetic drugs in terms of efficacy and safety.

3. To generate a clinically useful ranking of antiemetic drugs (mono- and combination prophylaxis) according to efficacy and safety.

B A C K G R O U N D

Description of the condition

Postoperative nausea and vomiting (PONV) is one of the major and most frequently observed problems anaesthetists and patients have to face after surgical procedures. In the majority of cases,

PONV occurs during the first 24 hours postoperatively with a peak in the immediate postoperative hours (Apfel 2002). About 30% of all patients undergoing anaesthesia using volatile anaesthetics without prior prophylaxis are affected by PONV after surgery (Apfel 1999). Apfel and colleagues developed a simplified score in 1998 that helps to predict the individual risk for the occurrence of PONV in adults. The four risk factors included are: female gender; non-smoker status; a history of PONV or motion sickness; and

expected postoperative opioid use. Apfel suggests the likelihood of PONV ranges from 10% (no risk factors present) to 79% (all four risk factors present) (Apfel 1999).

Rarely described but serious consequences of PONV that are usually secondary to vomiting include aspiration pneumonia, Boerhaave's syndrome, and severe subcutaneous emphysema (Attalah 2004; Baric 2000; Kranke 2011; Reddy 2008; Schumann 1999). However, PONV is an unpleasant feeling associated with discomfort and is a burdensome side effect for patients receiving anaesthesia (Kranke 2011). It is subjectively rated to be as serious as postoperative pain and has an important influence on the quality of recovery (Hocking 2013; Kranke 2011). Moreover, PONV can lead to prolonged or unexpected hospital stay or even readmission, and interferes with early postoperative recovery (Kranke 2011).

Description of the intervention

A huge variety of antiemetic drugs, grouped into six different drug classes, are available for the prevention of PONV (Gan 2007a;

Gan 2014; Horn 2014; Wiesmann 2015): 5-HT$_3$ receptor antagonists (e.g. ondansetron, dolasetron, granisetron, tropisetron,

ramosetron, palonosetron, and tandospirone); D$_2$ receptor antagonists (e.g. droperidol, haloperidol, metoclopramide, perphenazine, amisulpride, alizapride, bromopride, chlorpromazine, domperidone, prochlorperazine, sulpiride, tiapride, trimeprazine,

and trimethobenzamide); NK$_1$ receptor antagonists (e.g. aprepitant, casopitant, rolapitant, fosaprepitant, CP-122,721, netupitant, and vestipitant); corticosteroids (e.g. dexamethasone, methylprednisolone, and betamethasone); antihistamines (e.g. dimenhydrinate, meclizine, promethazine, and cyclizine); and anticholinergics (i.e. transdermal scopolamine).

The six different substance classes are characterised by varying adverse effects: 5-HT$_3$ receptor antagonists (e.g. headache

and constipation); D$_2$ receptor antagonists (e.g. extrapyramidal symptoms, sedation, arrhythmia, and QT prolongation); corticosteroids (e.g. hyperglycaemia, immunosuppression, and wound healing deficits); antihistamines (e.g. drowsiness, xerostomia, and urinary tract difficulties); and anticholinergics (e.g. dry mouth and visual disturbances) (Gan 2014; Horn 2014; Wiesmann 2015). There is currently limited evidence on adverse effects belong-

ing to NK$_1$ receptor antagonists; however, increased dizziness or headache were described by individual studies (Diemunsch 2009). Drugs with different mechanisms of action should be used in combination to optimise efficacy (Gan 2007b). For example, the 5-

HT$_3$ antagonists, which have better anti-vomiting than anti-nausea efficacy (yet are associated with headache), can be used in combination with droperidol, which has greater anti-nausea efficacy and a protective effect against headache (Gan 2007b).

In addition to drugs with direct antiemetic action, there are several other strategies for PONV prophylaxis available - which are not in the focus of the current protocol - such as drugs with indirect opioid-sparing effects (e.g. gabapentin; Grant 2016), or strategies such as reducing the emetic potency of the anaesthesia itself (for example by using propofol; Apfel 2004), and also non-pharmacologic prophylaxis strategies (e.g. stimulation of the wrist acupuncture point PC6; Lee 2015).

The Gan 2014 'Consensus guidelines for the management of postoperative nausea and vomiting' give information about current options for the prevention and treatment of PONV including both pharmacologic and non-pharmacologic regimen comprising the most commonly used antiemetic drugs, doses and timing of application. With adequate prophylaxis, one antiemetic agent can reduce the likelihood (relative reduction) of PONV by 25% (Gan 2014). This evidence-based guideline currently recommends one to two interventions for PONV prophylaxis for patients at moderate risk (Gan 2014).

It is important to provide adequate prophylaxis regarding type and time of application. With respect to varying duration of surgery and the need for a reasonably effective drug level at the 'time of risk' in the postoperative setting, the intravenous or parenteral application of antiemetics in accordance with their pharmacokinetic profile may be appropriate. The large majority of antiemetic drugs are usually administered by a slow intravenous push or as an infusion administered over a short period of time.

How the intervention might work

Five of the six substance classes with direct antiemetic effects mostly differ in their antagonistic action against different emetogenic substances at specific receptors, for example in the area postrema or on the free nerve endings of the vagus nerve (Gan 2007a; Gan 2014; Horn 2014; Wiesmann 2015). :

1. 5-HT$_3$ receptor antagonists: high levels of the neurotransmitter serotonin (5-hydroxytryptamin, 5-HT) induce nausea and vomiting by activating the specific receptors in the gut and central nervous system. Drugs belonging to this substance class inhibit serotonin receptors centrally and peripherally.

2. D$_2$ receptor antagonists: dopamine antagonists work as antiemetics in small dosages by blocking central dopamine receptors.

3. NK$_1$ receptor antagonists: the neurotransmitter substance P binds to the Neurokinin 1-receptor in the area postrema and

thereby induces nausea and vomiting. NK$_1$ receptor antagonists block these receptors and inhibit this pathway.

4. Antihistamines (Histamine 1 receptor antagonists): the tissue hormone histamine induces nausea and vomiting by

activating central H_1-receptors. Antihistamines for the use of PONV prevention predominantly block these receptors but also have anticholinergic effects.

5. Anticholinergics: anticholinergic agents have a parasympatholytic effect by inhibiting the binding between the neurotransmitter acetylcholine and the muscarinic receptor centrally.

The sixth group of antiemetics with direct antiemetic effects consists of corticosteroids. It is not exactly known how corticosteroids exert their antiemetic effect. Some theories assume that the anti-inflammatory impact and the decrease of arachidonic acid release reduce the occurrence of PONV.

Why it is important to do this review

Preventing PONV is important for patients' well being and is one major factor influencing satisfaction with anaesthesia. Therefore, it is important for patients to be provided with sufficient antiemetic prophylaxis. Besides, PONV is a major contributor to direct and indirect healthcare costs (Eberhart 2014; Hirsch 1994). Among others, these include costs for prolonged stay in recovery rooms and costs due to extra nursing time needed for PONV patients (Hirsch 1994; Smith 2012). Especially in a time when healthcare resources are scarce and the healthcare workforce is decreasing, the correct prophylaxis offers an advantage. Many antiemetics have proven efficacy in clinical use. Unfortunately, the use of prophylactic antiemetics for patients at risk is not part of the daily routine of all anaesthetists due to inadequate implementation of the risk-adapted approach in some clinical departments (Franck 2010).

Moreover, risk‐benefit issues remain a subject of debate in the anaesthesia community and the fear of possible adverse effects may be another reason for restraint (Kranke 2011).

There are many studies that investigate not only monotherapy but also the combination of antiemetics in order to reduce the likelihood of developing PONV. Trials examining different doses or dose ranges from one or more drugs administered in various ways (intravenous, intramuscular, oral, transdermal) create a wide spectrum of information that is difficult to assess based on simple direct comparisons.

Carlisle and Stevenson performed a systematic review in 2006 assessing all available drugs with antiemetic action for preventing PONV in adults and children in terms of efficacy and side effects, and included more than 700 studies with over 100,000 participants (Carlisle 2006). All trials reporting PONV as an outcome and comparing a drug with placebo, no treatment or another drug, or comparing different dosing or timing of administration were included. This review contained a large number of direct comparisons since no restrictions regarding study population or type of intervention were defined.

Recently, Tricco and colleagues published a systematic review with network meta-analysis (NMA) dealing with the efficacy and safety of serotonin receptor antagonists compared to each other, placebo and in combination with other antiemetic agents for PONV prevention (Tricco 2015a; Tricco 2015b). However, no other substance classes were examined.

Despite the continuing flood of clinical trials on PONV prophylaxis (estimated at more than 1000 studies) there is still no current overview of all relevant substance classes. There is a lack of direct comparisons of frequently used antiemetics and a lack of a clinically useful ranking of all antiemetic drugs with respect to both efficacy and safety. The Carlisle review of PONV needs an update (Carlisle 2006). However, the original review was withdrawn in 2017, partly because several included studies were retracted since publication (Carlisle 2017). Another reason is that the literature is now so large and complex that a very large series of direct comparisons - as performed in the Carlisle review of PONV - would be a task, and even more difficult to comprehend. Thus, a new and more efficient approach is needed to allow readers to readily appreciate the best-quality evidence available. For the current review, we will perform an NMA that allows comparison of antiemetic drugs in a direct and indirect manner (see Methods). The aim of this review is to generate a clinically useful ranking of antiemetic drugs (mono- and combination prophylaxis). It is also to provide clear information for patients and physicians by which to guide clinical decisions that enhance efficacy on the one hand and reduce the occurrence of side effects on the other. To enhance feasibility, we made a pre hoc decision to focus on the six clinically relevant drug classes with direct antiemetic action currently used or under investigation. For example, drugs like gabapentin that exert an antiemetic effect in an indirect way via an opioid-sparing effect (Grant 2016) or non-pharmacologic interventions (Lee 2015) are not within the focus of the review. The review will be restricted to adult patients and to studies published in full. This systematic review is deliberately designed to address some of the questions raised by the current PONV guideline (Gan 2014), with the aim of providing an evidence-based basis for future updates to this guideline.

This protocol is based on the PRISMA Extension Statement for NMA (Hutton 2015); and on the 'Protocol template for a Cochrane Intervention review that compares multiple interventions' from the Cochrane Comparing Multiple Interventions Methods Group (Protocol Template 2014).

OBJECTIVES

1. To compare the efficacy and safety of different prophylactic pharmacological interventions (antiemetic drugs) either against no treatment, placebo or against each other (as mono- or combination prophylaxis) for the prevention of postoperative nausea and vomiting in adults undergoing any type of surgery under general anaesthesia.

2. To explore the best dose or dose range of the antiemetic drugs in terms of efficacy and safety.

3. To generate a clinically useful ranking of antiemetic drugs (mono- and combination prophylaxis) according to efficacy and safety.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomized controlled trials (RCTs) that compare one or more antiemetics for the prevention of PONV against no treatment, placebo or another antiemetic drug. We will exclude quasi-randomized trials (trials in which treatment allocation is achieved by date of birth, alternation, or similar predictable methods).

We will include trials in which allocation to treatment may not have been adequately concealed but we will consider trial methodological quality in data analyses and interpretation.

We will not restrict inclusion based on language of publication. Retracted studies and studies authored by Fujii and colleagues will not be included into the review (Kranke 2000; Tramer 2013). Eligible studies must be reported in full text and published in a peer-reviewed journal. Since we expect to identify more than 1000 full-text, peer-reviewed studies we will exclude studies published in abstract form only to reduce the workload and to enhance feasibility of the review in a reasonable time frame.

Types of participants

We will only include trials that analyse adult participants ($\geq$ 18 years) undergoing any type of surgery under general anaesthesia. Studies with children only or mixed populations where data of children and adults cannot be separated will not be included in the review. We will not include studies using regional or sedative anaesthetic techniques.

Types of interventions

We will include studies that compare any pharmacological intervention(s) with antiemetic action belonging to one of the following drug classes versus each other or versus no treatment or placebo.

1. 5-HT$_3$ receptor antagonists.

2. D$_2$ receptor antagonists.

3. NK$_1$ receptor antagonists.
4. Corticosteroids.

5. Antihistamines (Histamine 1 receptor antagonists).
6. Anticholinergics.

For future updates, we may also include emerging drugs from other drug classes if it has been demonstrated they exert a direct antiemetic action.

We will also include trials that analysed combinations of antiemetic drugs, whereby each combination represents a separate intervention of interest and therefore a separate node in the NMA (splitting). In the run-up to the NMA, we will assess the geometry of the network (all interventions (mono- and combination prophylaxis) versus mono-prophylaxis alone). We aim to examine all possible combination prophylaxis in case geometry of the network allows this holistic approach. Otherwise we will split the disconnected network and analyse the single networks separately.

Different doses of drugs will be combined into one node (lumping). Dose effects will be analysed in subgroup analysis in case of heterogeneity/inconsistency.

Not all eligible interventions from the various drug classes are of primary interest regarding their effect. All drugs of primary interest for the review are listed in the section 'Interventions of direct interest'. Eligible interventions not of direct interest will be included in the network to increase the amount of available (indirect) information in the analysis (see 'Inclusion of additional interventions to supplement the analysis') (Ades 2013; Protocol Template 2014).

The antiemetic drug(s) have to be administered before the onset of postoperative nausea and vomiting. The drug(s) can be given preoperatively, at induction of anaesthesia or during anaesthesia. Participants in all treatment arms within a study must be subject to the same anaesthesia regimen with comparable dosing since the anaesthesia management itself may have influence on the incidence of PONV. For studies that report results separately for varying baseline anaesthesia regimens, the different regimens will not be combined, but considered as sub-studies.

We assume that any participant who meets the inclusion criteria is, in principle, equally likely to be randomized to any of the eligible interventions.

Interventions of direct interest

Antiemetic drugs of direct interest in the current review are either those recommended in the 'Consensus guidelines for the management of postoperative nausea and vomiting' (Gan 2014) or promising, emerging substances such as fosaprepitant and amisulpride. Emerging drugs will be considered as 'Interventions of direct interest' if they were investigated in more than two studies with more than 400 patients published in the last five years before the search date. Otherwise, they will be analysed as 'Additional interventions to supplement the analysis'.

1. 5-HT$_3$ receptor antagonists: ondansetron, dolasetron, granisetron, tropisetron, ramosetron, and palonosetron

2. D$_2$ receptor antagonists: droperidol, haloperidol, metoclopramide, perphenazine, and amisulpride

3. NK$_1$ receptor antagonists: aprepitant, casopitant, rolapitant, and fosaprepitant

4. Corticosteroids: dexamethasone, methylprednisolone

5. Antihistamines (Histamine 1 receptor antagonists): dimenhydrinate, meclizine, promethazine

6. Anticholinergics: transdermal scopolamine

We will restrict all explorative analyses and the rating of the quality of evidence to the interventions of direct interest and report the findings in detail in this review.

Inclusion of additional interventions to supplement the analysis

Eligible interventions which are not of direct interest will be included in the network to increase the amount of available (indirect) information in the analysis. The following antiemetic drugs could be relevant:

1. 5-HT$_3$ receptor antagonists: e.g. tandospirone.

2. D$_2$ receptor antagonists: e.g. alizapride, bromopride, chlorpromazine, domperidone, prochlorperazine, sulpiride, tiapride, trimeprazine, and trimethobenzamide.

3. NK$_1$ receptor antagonists: e.g. CP-122,721, netupitant, and vestipitant.

4. Corticosteroids: e.g. betamethasone.

5. Antihistamines (Histamine 1 receptor antagonists): e.g. cyclizine.

6. Anticholinergics: no drug for this class in this category is pre-specified.

The results will only be reported in the supplementary material (e.g. Appendices).

Types of outcome measures

Primary outcomes

We will estimate the relative effects of the competing interventions according to the following primary outcomes:

1. Vomiting (or dry retching) within 24 hours postoperatively: we will only include studies in the analysis that report events in an observation period of 0 to 24 hours ± 6 hours postoperatively.

2. Serious adverse events (SAEs): number of participants with at least one SAE (as defined in the study) in the observation period (up to seven days).

3. Any adverse event (AE): number of participants with at least one AE (as defined in the study) in the observation period (up to seven days).

We will estimate the relative ranking of the competing interventions according to the primary outcomes.

Secondary outcomes

We will estimate the relative effects of the competing interventions according to the following secondary outcomes:

1. 'Early' postoperative vomiting (or dry retching): studies with an observation period starting immediately after anaesthesia and ending two to six hours later (or defined as PACU).

2. 'Late' postoperative vomiting (or dry retching): studies with an observation period within the range of two to 24 hours postoperatively. If studies recorded the outcome during different periods of the two to 24 hour postoperative period but then did not report the risk for the complete observation period (two to 24 hours), we will report the risk of the outcome once for each study using the risk for the period in which the outcome was most common (all groups combined).

3. Nausea within 24 hours postoperatively: we will only include studies into the analysis that report an observation period of 0 to 24 hours ± 6 hours postoperatively. Studies that have reported the combined endpoint PONV only (and not nausea separately) are considered as nausea. We will not include continuous data on nausea such as grades of nausea measured on appropriate scales into the analysis.

4. Mortality: number of participants who have died in the observation period (up to seven days).

5. Arrhythmia: number of participants with an arrhythmia (as defined by the trialists) in the observation period (up to seven days).

6. QT prolongation: number of participants with a QT prolongation (as defined by the trialists) in the observation period (up to seven days).

7. Extrapyramidal symptoms: number of participants with extrapyramidal symptoms (e.g. dystonia, dyskinesia, akathisia, bradykinesia, tremor) in the observation period (up to seven days).

8. Postoperative wound infection: number of participants with postoperative wound infections in the observation period (up to seven days).

9. Headache: number of participants with headache in the observation period (up to seven days).

10. Constipation: number of participants with constipation in the observation period (up to seven days).

11. Sedation/drowsiness: number of participants with sedation/drowsiness in the observation period (up to seven days).

12. Visual disturbances: number of participants with visual disturbances (e.g. blurred vision) in the observation period (up to seven days).

Search methods for identification of studies

We will search for all possible comparisons formed by the research question.

Electronic searches

We will identify RCTs through literature searching designed to identify relevant trials as outlined in Chapter 6.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will not apply language restrictions.
We will search the following databases for relevant trials.

- Cochrane Central Register of Controlled Trials (CENTRAL) (latest Issue).
- MEDLINE (Ovid SP, 1946 onwards).
- Embase (Ovid SP, 1974 onwards).
- CINAHL via EBSCO host (1982 to present).

We developed a draft search strategy for MEDLINE. The search strategy can be found in Appendix 1 and will be used as the basis for the search strategies in the other databases listed.

We will scan the following trials registries for ongoing and unpublished trials.

- ClinicalTrials.gov.
- WHO ICTRP.

Since we expect to identify more than 1000 full texts of peer-reviewed studies by searching the above-mentioned electronic databases, we will not search other resources such as conference proceedings, nor will we include abstracts, to reduce the workload and to enhance feasibility of the review in a reasonable time frame.

Searching other resources

We will scan the reference lists and citations of included trials and any relevant systematic reviews identified for further references to additional trials.
When necessary we will contact trial authors for additional information.

Data collection and analysis

Selection of studies

We will use Covidence, a web-based software platform (Covidence), for the process of study selection. All records identified with the search strategy described above will be imported into Covidence. The following review authors will participate in the screening of records: SW, YJ, PKr, ILB, DR, LE, MS, PKi. In each case two of them will independently screen the title and abstract of an individual record for eligibility using a predefined eligibility checklist (Appendix 2). For all potentially relevant records, we will retrieve the full texts to finally decide which studies satisfy the inclusion criteria. All full texts will be reviewed by two independent review authors. We will resolve discrepancies in judgements by discussion with a third author.

Data extraction and management

Two independent review authors will extract the data using a predefined data extraction form (Appendix 3) in the Covidence environment (Covidence) including data on outcomes, on potential effect modifiers and on other data. The following review authors will participate in the screening of records: SW, YJ, PKr, ILB, DR, LE, MS, PKi. We will resolve discrepancies in judgements by discussion with a third author. We will export data from Covidence into Review Manager software (Review Manager 2014) and check for accuracy.

Outcome data

We will extract from each included study all data relevant to the primary and secondary outcomes listed in the section 'Types of outcome measures'.
We will extract arm-level data when possible. When arm-level data are not available we will extract effect sizes.
We will extract the following characteristics associated with the monitoring and reporting of (severe) adverse events in each primary study.

- Type of monitoring for SAEs/AEs (active or spontaneous).
- Type of monitored AEs (defined AEs/any AEs).
- Use of an accepted international classification for SAEs (e.g. according to 'The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use' (ICH) guidelines).
- Number of SAEs reported (yes/no).

Data on potential effect modifiers

From each included study we will extract data on the following potential effect modifiers.

- Population and baseline characteristics (gender; smoking status; history of PONV/motion sickness; type of surgery; type of anaesthesia; duration of anaesthesia; and use of perioperative opioids).
- Intervention (dose; time point of administration (early versus late (after incision)); route of administration).
- risk of bias (allocation concealment; blinding of participant, personnel and outcome assessors; incomplete outcome data)
- funding source (sponsorship source and involvement)

We will use these characteristics for the evaluation of the transitivity assumption.

Other data

We will extract from each included study data on the following additional information.

- Identification (year of publication; journal; first author (with contact information); location of study conduct; number of centres; duration of study; trial registry number).
- methods (study design, groups).
- population (inclusion and exclusion criteria with group differences; participant flow (number of participants assessed for eligibility, randomized, received treatment, and analysed))

Review of network geometry

We will graphically evaluate the geometry of the whole network including interventions of direct interest (mono- and combination prophylaxis) and any other intervention in which we are not directly interested (see 'Inclusion of additional interventions to supplement the analysis') (Rucker 2016). We will use the information of the network geometry to determine whether a network meta-analysis is feasible for all interventions or only for sub-networks (e.g. mono-prophylaxis).

Assessment of risk of bias in included studies

We will assess the risk of bias for each included study by using the Cochrane 'Risk of bias' assessment tool 1.0 (Higgins 2011). The standard domains include random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessors; incomplete outcome data; selective reporting; and any other bias. We will judge each component as being 'low risk of bias', 'high risk of bias' or 'unclear risk of bias'. We will include a 'Risk of bias' table as part of the 'Characteristics of included studies' table and 'Risk of bias summary'/'Risk of bias graph' figures, which will detail all of the judgements made for all included studies in the review.

We will also assess the characteristics associated with the monitoring and reporting of (severe) adverse events in each primary study and report this information in an additional table - 'Assessment of adverse event monitoring' - along with a judgement on the risk of bias as described by Tramacere and colleagues (Tramacere 2015). Two review authors will independently perform the study quality assessment using a predefined critical appraisal form in the Covidence environment (Appendix 4). We will resolve any disagreements by discussion with a third author.

1. Random sequence generation

We will consider sequence generation as adequate if it was generated by a random system (for example computer, random number table algorithm, tossing of a coin). We will consider sequence generation inadequate if a non-random system was used (for example names, dates). Those quasi-randomized trials will be excluded. We

will assess the study as 'unclear risk of bias' if the only information about randomization is that the study was randomized.

2. Allocation concealment

We will consider concealment adequate if an acceptable method, such as a central allocation system, sequentially numbered sealed opaque envelopes (SNOSE) or an on-site locked computer, was used to ensure that the group assignment was not revealed to patient recruiters, investigators or participants prior to the final allocation into the respective group. We will consider concealment to be inadequate if it allowed the patient recruiters, investigators or participants to know the treatment allocation in advance, and we will assess the study as 'unclear risk of bias' if the concealment procedure was not reported.

3. Blinding of participants and personnel outcome assessors

We will consider blinding adequate if participants and personnel (e.g. anaesthetists) were all blinded to the intervention. We will consider blinding inadequate if participants and personnel were not blinded to the intervention.

4. Blinding of outcome assessors

We will consider blinding adequate if outcome assessors were all blinded to the intervention. We will consider blinding inadequate if outcome assessors were not blinded to the intervention.

4. Incomplete outcome data

We will consider the domain 'incomplete outcome data' as adequate if the number of dropouts is 15% or less, and balanced between arms; and the reasons for dropouts are reported, and appear to be unrelated to the studied outcomes. We will consider outcome data as incomplete if the number of dropouts is greater than 15%, or significantly imbalanced between groups, or the reasons for dropouts are not reported, or appear to be related to the outcomes of interest in the study.

5. Selective outcome reporting

We will assess selective outcome reporting by comparing the type and order of outcomes (primary versus secondary) reported in the study protocol along with the published outcomes. We will consider outcome reporting as adequate if a prospectively registered study protocol is available and all predefined primary and secondary outcomes are also reported in the published study. We will judge selective outcome reporting as 'high risk of bias' if the predefined primary outcomes in the registered protocol differ from those in the published study report. If there is no prospectively registered study protocol available, we will assess selective outcome reporting as 'unclear risk of bias'.

6. Other sources of bias

Other potential risk of bias include baseline imbalance in factors that are strongly related to outcome measures and can cause bias in the intervention effect estimate.

Overall risk of bias summary

We will summarize the risk of bias for each study depending on the judgements for the domains 'allocation concealment', 'blinding of participant, personnel, and outcome assessors', and 'incomplete outcome data'. We will classify each study as 'low risk of bias' when we judge all of the domains as 'low risk of bias'. If we judge at least one domain as 'high risk of bias' or all domains as 'unclear risk of bias', we will classify the overall risk of bias for the study as 'high risk of bias'. In the remaining cases we will classify the study as 'unclear risk of bias'. We will use the information of the 'Overall risk of bias summary' for sensitivity analyses.

Assessment of adverse event monitoring

The way of monitoring adverse events may introduce bias to the relevant adverse outcomes. Therefore, we will assess the risk of bias associated with monitoring for adverse events. We will evaluate the methods of monitoring for adverse events in each primary study on the basis of the following questions as described by Tramacere and colleagues with some modifications (Tramacere 2015).

1. Did the authors actively monitor for AEs (any AE)?
2. Did the authors simply provide spontaneous reporting of AEs that arose?
3. Did the authors only actively monitor for defined AEs and other relevant AEs were not monitored?
4. Did the authors define SAEs according to an accepted international classification and report the number of SAEs?

We will not include this information in the 'Risk of bias' table. We will report this information in an additional table 'Assessment of adverse event monitoring' along with a judgement of the risk of bias (Tramacere 2015).

We will use the information from the assessment of adverse event monitoring to test the robustness of the effect estimates for the primary outcomes 'any SAE' and 'any AE' by sensitivity analyses (exclusion of 'high risk of bias' studies for adverse event monitoring).

Measures of treatment effect

Relative treatment effects

We will estimate the pairwise relative treatment effects of the competing interventions using the risk ratio (RR) with 95% confidence intervals (95% CIs) for each outcome.

Results from network meta-analyses will be presented as summary relative effects (RR) for each possible pair of treatments.

Relative treatment ranking

We will rank the competing treatments by P scores (Rucker 2015) using the R package netmeta (netmeta). P scores allow ranking of treatments on a continuous 0 to 1 scale and are derived from the P values of all pairwise comparisons. P scores are the frequentist analogue and numerically similar to the Bayesian SUCRA values (Rucker 2015).

We will look at comparative efficacies between the antiemetic drugs and express this using placebo as a reference compound.

Unit of analysis issues

Cluster-randomized trials

We will not include cluster-randomized trials.

Cross-over trials

We will not include trials with cross-over design.

Studies with multiple treatment groups

We will include multi-arm studies in the data set as a series of two-arm comparisons. To reflect the fact that comparisons within multi-arm studies are correlated, we will adjust the standard error of each two-arm comparison from a multi-arm study. We will use the method proposed by Rücker and Schwarzer which uses back-calculated standard errors in the weighted least-square estimator to reflect the within-study correlation (Rucker 2012; Rucker 2014; Rucker 2015).

Studies with zero events

We will include studies with zero events in one or more arms into the analysis. We will apply the constant continuity correction approach (continuity correction 0.5) using the R software.

Dealing with missing data

We will note levels of attrition for included studies. Since we expect to identify more than 1000 studies we will use published data only and will not request missing outcome data from the trials' authors, to reduce the workload and to enhance feasibility of the review in a reasonable time frame. We will explore the impact of excluding studies (sensitivity analysis) with unclear or high risk of bias for incomplete outcome data in the overall assessment of treatment effects.

We will carry out analyses for efficacy outcomes, as far as possible, on an intention-to-treat (ITT) basis. For analysis of safety, we will carry out as-treated analysis as far as possible (and we are ready to accept if the randomization is broken).

In case of missing data, we will use an 'available-case analysis' by excluding all participants from the analysis for whom the outcome is missing.

Assessment of heterogeneity

Assessment of clinical and methodological heterogeneity within treatment comparisons

We will use descriptive statistics reported in the 'Characteristics of included studies' table to assess whether the studies within each pairwise comparison are homogenous enough with respect to study and population baseline characteristics (see data extraction form 'Potential effect modifiers') so that the assumption of homogeneity might be plausible. In case of excessive clinical heterogeneity we will not pool the findings of the included studies.

Assessment of transitivity across treatment comparisons

We will assess the assumption of transitivity by comparing the distribution of potential effect modifiers (see data extraction form 'Potential effect modifiers') across the different pairwise comparisons. In case of intransitivity (e.g. substantially imbalanced distribution of effect modifiers) we will not include those studies in any NMA.

Assessment of reporting biases

Where there are 10 or more relevant studies, we will investigate risk of bias across studies (such as publication bias) in pairwise meta-analyses ('Interventions of direct interest', primary outcomes) using contour-enhanced funnel plots. If funnel plot asymmetry is suggested by a visual assessment, we will perform exploratory analyses (e.g. Rücker's arcsine test for dichotomous data) to further investigate funnel plot asymmetry. We will analyse reporting bias using the R package metasens.

Data synthesis

Methods for direct treatment comparisons

We will perform standard pairwise meta-analyses using a random-effects model (inverse variance weighting) in R for each treatment comparison with at least two studies. We will use the random-effects model, as we expect methodological and clinical heterogeneity across the included studies resulting in varying effect sizes between studies of pairwise comparisons.

Methods for indirect and mixed comparisons

We will perform random-effects NMAs for all outcomes basing on a frequentist framework in R using the package netmeta version 0.9 to 3-5 or newer (Rucker 2014). For separating direct and indirect evidence, we will use the function netsplit from this package.

Methods for analysing combinations of drug

The primary NMA will treat all mono-prophylaxis and all combination prophylaxis as different nodes in the network. We will perform a second analysis based on the assumption that the effects of combined treatments (e.g. A + B, A + B + C, B + C) are additive sums of their components. This assumption, together with the network structure, leads to a statistical model that allows decomposing the observed relative effects into the single components and estimating the effects of the components. The hypothesis of additivity can be tested by comparing the estimates from this model with those from the primary analysis (Mills 2012).

Subgroup analysis and investigation of heterogeneity

Assessment of statistical heterogeneity

Assumptions when estimating the heterogeneity

In NMA we will assume the same heterogeneity across the different comparisons. In standard pairwise meta-analyses we will assume the common heterogeneity variance estimated from the NMA for each pairwise comparison.

Measures and tests for heterogeneity

We will assess heterogeneity by the common between-trial variance (tau^2), the Q-test, and the I^2 statistic.

Assessment of statistical inconsistency

Inconsistency is the statistical manifestation of intransitivity and occurs when the direct and indirect estimates in a network of treatments do not agree. The distinction between intransitivity and inconsistency is analogous to the distinction between clinical (or methodological) heterogeneity and statistical heterogeneity in standard pairwise meta-analysis (Cipriani 2013). We will assess heterogeneity and inconsistency by decomposing the Q statistic into variation of the effect estimates within designs (heterogeneity) and between designs (inconsistency) (Higgins 2012; Krahn 2013). In addition, to locate sources of inconsistency, we will create and examine a net heat plot (Krahn 2013). For Q decomposition and creation of the net heat plot, we will use the R package netmeta. In addition, we will assess differences between direct and indirect effect estimates using descriptive z-tests.

Investigation of heterogeneity and inconsistency

If we find substantial to considerable heterogeneity or inconsistency (or both), we will explore the possible sources (Higgins 2011). If sufficient studies are available, we will perform subgroup analyses using potential pre-specified effect modifiers (see data extraction form 'Potential effect modifiers') as source of heterogeneity or inconsistency (or both). We will restrict these explorative analyses to the primary outcomes. For pairwise comparisons, we will use the R package meta for subgroup analyses or meta-regression analyses. For the network, we will use the R package netmeta to do separate analyses for the subgroups; however, the network will be different from that of the primary analysis and we cannot be sure that it remains connected.

Gender, non-smoking status, and history of PONV/motion sickness are patient-level characteristics. Those characteristics will be only analysed as effect modifiers in subsequent analyses, if the events (e.g. subjects who vomited) are separately reported (e.g. for men and women) to avoid the risk of ecological bias. If those characteristics are not separately reported, we will assess whether there is an imbalance in the distribution of these characteristics in the study's arms and use this information for sensitivity analyses (excluding studies from the meta-analyses with imbalance in the distribution of the relevant characteristics).

Different treatment regimens
dose

Since it is of interest for clinicians and patients to know the optimal dose of antiemetic drugs with respect to efficacy and safety, we will split different doses of the same drug into low, recommended and high doses (Table 1) and perform subgroup analyses. We will restrict splitting of doses to mono-prophylaxis and to the interventions of direct interest. The recommended doses or dose ranges for drugs are based on that reported in the 'consensus guidelines for the management of postoperative nausea and vomiting' (Gan 2014). For emerging substances, we will use doses or dose ranges based on dose-finding studies (e.g. for amisulpride see Kranke 2013; no data are available for fosaprepitant).

We will categorize the spectrum of available fixed doses into low, recommended and high doses according to the following algorithm.

1. If a single dose X is recommended (Gan 2014), we will define X as the 'recommended dose'; 'low dose' as < X; 'high dose' as > X (lower and upper limits will only be defined, if reported in Gan 2014).

2. If a dose range X to Y is recommended (Gan 2014), we will define X to Y as 'recommended dose range'; 'low dose' as < X; 'high dose' as > Y (lower and upper limits will only be defined if reported in Gan 2014).

If flexible doses (e.g. mg/kg) are reported, we will transform flexible doses into fixed doses by multiplying the flexible dose with the

mean/median weight of participants reported in the published study (if the weight is not reported, we will assume 70 kg).

We will use the R package netmeta to do separate analyses for the subgroups; however, the network will be different from that of the primary analysis and we cannot be sure that it remains connected. We will perform this explorative analysis ('dose') for all primary and for all secondary outcomes considering side effects in case of substantial to considerable statistical heterogeneity (Higgins 2011).

Sensitivity analysis

We will analyse the robustness of the effect estimates performing the following sensitivity analyses.

- Including only trials at low risk of bias in the overall risk of bias summary (see 'Overall risk of bias summary').
- Excluding trials with imbalance in baseline details in the study's arms.
- Excluding trials that analysed the outcomes 'vomiting' or 'nausea' not as primary endpoints.
- Comparability of doses: there is a possibility that some trials compare one drug at the upper limit of its therapeutic range (e.g. high dose) with another agent at the lower limit of its therapeutic range (e.g. low dose) within the same study. We plan to capture this study characteristic by adding a dichotomous variable indicating whether the dosages are comparable (low-low, recommended-recommended, high-high; see Table 1), and use this information for sensitivity analysis (Cipriani 2009).
- Adverse event monitoring: We will use the information on adverse event monitoring of studies to test the robustness of the effect estimates for the primary outcomes 'any SAE' and 'any AE' by sensitivity analyses (exclusion of high risk of bias studies for adverse event monitoring).

We will restrict sensitivity analyses to the primary outcomes with exception of 'Comparability of doses' which is relevant for all side effects (secondary outcomes).

Summary of findings table and GRADE

We will present the main results of the review in 'Summary of findings' (SoF) tables including a rating of the quality of evidence based on the methodology developed by the GRADE Working Group (www.gradeworkinggroup.org/).

We will create six SoF tables, one for each substance class, comparing the drugs of direct interest (see 'Interventions of direct interest') as mono-prophylaxis to placebo including all primary outcomes and drug-class important adverse effects.

In the SoF tables we will present direct evidence, indirect evidence, and NMA evidence as well as ranking of treatments using P-scores. The quality of the body of evidence reflects within-study risk of bias (methodological quality), indirectness, heterogeneity of the data (inconsistency), imprecision of effect estimates, and risk of

publication bias. GRADE assessment will be performed by two independent reviewers.

The GRADE assessment results in one of four levels of 'quality', and these express our confidence in the estimate of effect (Balshem 2011).

- High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
- Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Quality of evidence for effect estimates can vary greatly across comparisons within a network, and can range from high to very low quality. In making inferences regarding the choice of an intervention, recognizing the quality of each comparison is far more valuable than ranking efficacy alone (Puhan 2014).

We will use the four-step approach presented by Puhan and colleagues to rate the quality of evidence in each of the direct, indirect, and network meta-analysis estimates based on methods developed by the GRADE Working Group (Puhan 2014).

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* Indicates the major publication for the study

ADDITIONAL TABLES

Table 1. Recommended, low, and high doses of antiemetic drugs

Drug	Dose*	Cut-off (lower, upper limit)**	Low dose	Recommended dose	High dose
Amisulpride	5 mg to 10 mg IV	NR	< 5 mg	5 mg to 10 mg	> 10 mg
Aprepitant	40 mg per os	NR	< 40 mg	40 mg	> 40 mg
Casopitant	150 mg per os	NR	< 150 mg	150 mg	> 150 mg
Dexamethasone	4 mg to 5 mg IV	NR	< 4 mg	4 mg to 5 mg	> 5 mg
Dimenhydrinate	1 mg/kg IV	NR	< 1 mg/kg	1 mg/kg	> 1 mg/kg
Dolasetron	12.5 mg IV	NR	< 12.5 mg	12.5 mg	> 12.5 mg
Droperidol	0.625 mg to 1.25 mg IV	See FDA[1] 2.5 mg IV	< 0.625 mg	0.625 mg to 1.25 mg	> 1.25 mg
Fosaprepitant	NR	NR	NR	NR	NR
Granisetron	0.35 mg to 3 mg IV	NR	< 0.35 mg	0.35 mg to 3 mg mg	> 3 mg
Haloperidol	0.5 mg to < 2 mg IM/IV	See FDA < 2 mg	< 0.5 mg	0.5 mg to < 2 mg	2 mg (cut-off)
Meclizine	50 mg per os	NR	< 50 mg	50 mg	> 50 mg
Methylpred-nisolone	40 mg IV	NR	< 40 mg	40 mg	> 40 mg
Metoclopramide	25 mg to 50 mg IV	10 mg[2]	< 25 mg (10 mg cut-off)	25 mg to 50 mg	> 50 mg

Table 1. Recommended, low, and high doses of antiemetic drugs (*Continued*)

Ondansetron	4 mg IV, 8 mg ODT	NR for PONV (32 mg for other[3])	< 4 mg IV, < 8 mg ODT	4 mg IV, 8 mg ODT	> 4 mg IV, > 8 mg ODT, (32 mg cut-off)
Palonosetron	0.075 mg IV	NR	< 0.075 mg	0.075 mg	> 0.075 mg
Perphenazine	5 mg IV	NR	< 5 mg	5 mg	> 5 mg
Promethazine	6.25 mg to 12.5 mg IV	NR	< 6.25 mg	6.25 mg to 12.5 mg	> 12.5 mg
Ramosetron	0.3 mg IV	NR	< 0.3 mg	0.3 mg	> 0.3 mg
Rolapitant	70 mg to 200 mg per os	NR	< 70 mg	70 mg to 200 mg	> 200 mg
Scopolamine	Transdermal patch	NR	NA	NA	NA
Tropisetron	2 mg IV	NR	< 2 mg	2 mg	> 2 mg

* Recommended doses are based on Gan 2014; for amisulpride we used data from a dose-finding study (Kranke 2013).

** Cut-off limits are based on those reported in Gan 2014

[1] FDA black box warning

[2] Metoclopramide at a dose of 10 mg is not effective in reducing the incidence of PONV

[3] 32 mg single IV dose for chemotherapy-induced nausea (FDA warning)

Abbreviations: NR = not reported; NA = not applicable; ODT = orally disintegration tablets; IV = intravenous; IM = intramuscular; per os = per oral;

APPENDICES

Appendix 1. Search strategy (MEDLINE)

("nausea"[MeSH Terms] or nausea* or inappeten*) OR ("vomiting"[MeSH Terms] OR vomit* OR emesis OR emet* OR PONV) OR ("postoperative nausea and vomiting"[MeSH Terms])
AND
("postoperative period"[MeSH Terms] OR postoperative or post-operative) OR ("anesthesia"[MeSH Terms] OR anaesthesia OR anesthesia OR anaesthet* OR anesthet*)
AND
("antiemetics"[MeSH Terms] or antiemesis or anti-emesis or antiemetic* or anti-emetic* or antiemetogenic) OR (ALIZAPRIDE OR AMISULPRIDE OR APREPITANT OR BETAMETHASONE OR BROMOPRIDE OR CASOPITANT OR CHLOR-PROMAZINE OR CP-122,721 OR CYCLIZINE OR DEHYDROBENZPERIDOL OR DEXAMETHASONE OR DIMEN-HYDRINATE OR DOLASETRON OR DOMPERIDONE OR DROPERIDOL OR FOSAPREPITANT OR GRANISETRON OR HALOPERIDOL OR MECLIZINE OR MECLOZINE OR METHYLPREDNISOLONE OR METOCLOPRAMIDE

OR NETUPITANT OR ONDANSETRON OR PALONOSETRON OR PERPHENAZINE OR PREDNISOLONE OR PROCHLORPERAZINE OR PROMETHAZINE OR RAMOSETRON OR ROLAPITANT OR SULPIRIDE OR TANDOSPIRONE OR TIAPRIDE OR TRANSDERMAL SCOPOLAMINE OR TRIMEPRAZINE OR TRIMETHOBENZAMIDE OR TROPISETRON OR VESTIPITANT)
AND
(randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR randomised [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh])

Appendix 2. Eligibility checklist

Author (Year)				
Journal				
Title				
Is the study eligible?	Yes	No	Maybe	Note
Type of study				
RCT?				
Not quasi-RCT?				
Not cross-over study?				
Not retracted study (see clinicaltrials.gov) or authored by Fujii and colleagues?				
Not abstract only?				
Types of participants				
Adults ($\geq$ 18 yrs)?				
General anaesthesia?				
Types of intervention				
Monotherapy, or				
augmentation study (different class), or				
combination study (same class)?				

Substance class(es):	Name of drug(s):—————————————			
- 5-HT3 receptor antagonists				
- D_2 receptor antagonists				
- NK-1 receptor antagonists				
- Corticosteroids				
- Antihistamines				
- Anticholinergics				
Drug allocated before onset of PONV?				
Similar baseline anaesthesia regimen in study's arms?				

Appendix 3. Data extraction form

RCT Data Extraction	Notes
Identification	
Study details:	
First author	
Year of publication	
Journal	
Country (location of study conduct)	
Number of centres	
Duration of study (date)	
Trial registry number	

(Continued)

Author's contact details (corresponding author):	
Author's name	
e-mail address	
Methods	
Study design	
Groups	
Population	
Inclusion criteria	
Exclusion criteria	
Significant group differences (baseline imbalance)? (Y/N)	
Participant flow:	
# assessed for eligibility (n)	
# enrolled (n)	
# randomized (n/n)	
# received treatment (n/n)	
# analysed (n/n)	
Potential effect modifiers	
Population and baseline characteristics:	
Gender	
Non-smoker	
History of PONV/motion sickness	
Type of general anaesthesia	

Duration of anaesthesia	
Use of perioperative opioids (if yes, which?)	
Type of surgery	
Significant imbalance between groups? (Y/N) *If yes, please define.*	

Intervention	
Dose	
Time point of administration	
Route of administration	

Risk of bias (see Appendix 4: critical appraisal form)	
Allocation concealment	
Blinding of participant and personnel	
Blinding of outcome assessors	
Incomplete outcome data	

Funding source	
Sponsorship source	
Sponsorship involvement	

Outcome data

Type of outcome	Definition of outcome	Observation time period	Intervention (events)	Intervention (n)	Control (events)	Control (n)
Vomiting (0 to 24 hours)						

Vom-iting (0 to six hours)						
Vomiting (two to 24 hours)						
Nausea						
Sub-jects with any SAE						
Sub-jects with any AE						
Mortality						
Arrhyth-mia						
QT pro-longation						
Extrapyra-midal symptoms						
Postopera-tive wound infection						
Headache						
Constipa-tion						
Sedation/ drowsiness						
Vi-sual distur-bances (e. g. blurred vision)						

Monitoring and reporting of (severe) adverse events:

(Continued)

	Yes	No	Unclear	Risk of Bias	Note
Did the authors actively monitor for AEs (any AE)?					
Did the authors simply provide spontaneous reporting of AEs that arose?					
Did the authors only actively monitor for defined AEs and other relevant AEs were not monitored?					
Did the authors define SAEs according to an accepted international classification and report the number of SAEs?					

Appendix 4. Critical appraisal form

Author (Year)			
Journal			
Title			
Risk of Bias Assessment (with quotes and or statement)	*High Risk of Bias*	*Low Risk of Bias*	*Unclear Risk of Bias*
Random sequence generation (selection bias)			
State here the method used to generate the sequence			
Allocation concealment (selection bias)			
State here the method used to conceal allocation			
Blinding of participants and personnel (performance bias)			
Persons responsible for participants care			
Participants			
Blinding of outcome assessment (detection bias)			
Outcome assessor			
Incomplete outcome data (attrition bias)			
Adequate, if dropout rate ≤ 15% and balanced between arms and reasons for missing values reported, and unrelated to the analysed outcome (data analysis described and			

(Continued)

imputation methods correct)			
Selective reporting (reporting bias)			
Adequate, if a prospectively registered study protocol is available and all predefined primary and secondary outcomes are also reported in the published study			
Other bias			
Other sources of bias (e.g. imbalance in baseline characteristics between study's arms)			

CONTRIBUTIONS OF AUTHORS

Stephanie Weibel (SW), Yvonne Jelting (YJ), Nathan Leon Pace (NLP), Gerta Rücker (GR), Diana Raj (DR), Insa Linnea Backhaus (ILB), Maximilian S Schaefer (MSS), Peter Kienbaum (PKi), Leopold HJ Eberhart (LHJE), Peter Kranke (PKr)

Conceiving the review: SW, YJ, NLP, GR, DR, ILB, MSS, PKi, LHJE, PKr

Co-ordinating the review: SW

Undertaking manual searches: SW, YJ, DR, MSS

Screening search results: SW, YJ, DR, ILB, MSS, PKi, LHJE, PKr

Organizing retrieval of papers: SW, YJ, DR, ILB, MSS, PKi, LHJE, PKr

Screening retrieved papers against inclusion criteria: SW, YJ, DR, ILB, MSS, PKi, LHJE, PKr

Appraising quality of papers: SW, YJ, DR, ILB, MSS, PKi, LHJE, PKr

Abstracting data from papers: SW, YJ, DR, ILB, MSS, PKi, LHJE, PKr

Writing to authors of papers for additional information: SW, YJ

Providing additional data about papers: SW, YJ, DR, MSS

Obtaining and screening data on unpublished studies: SW, YJ, DR, MSS

Data management for the review: SW

Entering data into Review Manager 5 (RevMan 5): SW, YJ

RevMan statistical data: SW, GR, NLP

Other statistical analysis not using RevMan 5: SW, GR, NLP

Interpretation of data: SW, YJ, NLP, GR, DR, ILB, MSS, PKi, LHJE, PKr

Statistical inferences: SW, GR, NLP

Writing the review: SW, YJ, NLP, GR, DR, ILB, MSS, PKi, LHJE, PKr

Securing funding for the review: SW, PKr

Guarantor for the review (one author): PKr

Person responsible for reading and checking review before submission: SW, PKr

DECLARATIONS OF INTEREST

Stephanie Weibel has no conflict of interest regarding the topic of this review. Stephanie Weibel is an academic researcher. She has received personal payments for consultancies and lecture fees from Genelux Corporation, San Diego, USA (ended March 2014). Genelux Corp does not produce any products of the intervention of interest of this review. She was involved in the conduct of phase III clinical trials related to the current review ("Amisulpride (APD421)" in NCT02646566, NCT02449291, NCT02337062) and was involved in a meta-analysis on the incidence of postoperative nausea and vomiting published recently (Schaefer 2016).

Yvonne Jelting has no conflict of interest regarding the topic of this review. Yvonne Jelting is a clinical investigator and academic researcher. She was involved in the conduct of phase III clinical trials related to the current review ("Amisulpride (APD421)" in NCT02646566, NCT02449291).

Nathan L Pace has no conflict of interest regarding the topic of this review. Nathan L Pace is a non-practising anaesthetist and statistician faculty member of the University of Utah, receives no private practice income, and has no commercial relationships. He has received payment for development of educational presentations (Barash, Cullen, Stoelting CLINICAL ANESTHESIA 8th edition) and provided consultancy (St Marks Hospital, Salt Lake City, UT) on topics unrelated to the current review. He has received supplements to attend Cochrane meetings. He also has stocks and shares in companies who have no interest in the topic of this review (TIAA-CREF, Fidelity, Vanguard, USAA, MorganStanley).

Gerta Rücker is employed as a statistician at the Institute of Medical Biometry and Statistics of the Medical Center - University of Freiburg. She received payment for a one-day course on statistical methods in meta-analysis by Grünenthal Group, Aachen, Germany.

Diana Raj has no conflict of interest regarding the topic of this review. Diana Raj is a consultant in clinical anesthesiology.

Insa Linnea Backhaus has no conflict of interest regarding the topic of this review. Insa Linnea Backhaus is a healthcare economist.

Maximilian S Schaefer has no conflict of interest regarding the topic of this review. Maximilian S Schaefer is a post-doctoral fellow and resident in anesthesiology. He was involved in a meta-analysis on the incidence of postoperative nausea and vomiting published recently (Schaefer 2016).

Peter Kienbaum is employed as a clinical and academic anaesthetist and has been holding the position of vice chairman of the anaesthesia department for 10 years. His clinical and research work focuses on cardiovascular effects of anaesthetics and recovery after anaesthesia. He has been consulting for Baxter and Air Liquide with an interest in the marketing of inhalational anaesthetics and has received lecture fees from Orion Pharma. He authored several trial papers unrelated to the current review and was involved in a meta-analysis on the incidence of postoperative nausea and vomiting published recently (Schaefer 2016).

Leopold Eberhart is employed as a clinical and academic anaesthetist with a clinical and research focus on postoperative pain management and postoperative nausea and vomiting. He has received lecture fees (from Ratiopharm, Baxter) and has provided consultancy (to Ratiopharm, Grünenthal) on topics unrelated to the current review. He has received lecture fees to FreseniusKabi. This company manufactures propofol which may be effective as an antiemetic in reducing PONV. He has been involved in the conduct of phase II and phase III clinical trials related to the current review ("Amisulpride (APD421)" in NCT02646566, NCT02449291, NCT02337062, NCT01991821, NCT01510704; "Vestipitant (GW597599)" in NCT01507194; "Buspiron" in NCT00895830; IMPACT study (Apfel 2004)). He was author of several papers on postoperative nausea and vomiting.

SOURCES OF SUPPORT

Drugs for preventing postoperative nausea and vomiting in adults after general anaesthesia: a network meta-analysis (Protocol)   **25**

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